LEPTIN AND LEFT VENTRICULAR MASS IN A SOUTH AFRICAN POPULATION OF AFRICAN DESCENT

Neil Sookoo

A dissertation submitted to the Faculty of Medicine, University of the Witwatersrand, for the degree of Master of Science.

Johannesburg, 2009

ABSTRACT

Leptin is a substance that is released from adipose tissue and although it is primarily employed to modify body size, it also targets a number of other tissues, including the myocardium. Although plasma leptin concentrations may predict cardiovascular risk beyond conventional measurements, it is uncertain whether this may be explained by an independent effect on left ventricular mass (LVM) and geometry. Previous clinical studies evaluating the independent relationship between plasma leptin concentrations and LVM have been conducted in either small study samples (n=31-55), in severely obese participants only, in select subgroups (with insulin resistance) or in population samples with a relatively low mean body mass index (BMI). In the present dissertation I therefore assessed whether plasma leptin concentrations are associated with LVM and LV mean wall thickness independent of adiposity indices in 378 adults of African descent randomly recruited from a population sample with ~63% of people whom were either overweight or obese. LVM was determined using two-dimensional directed M-mode echocardiography and indexed to height$^{2.7}$ (LVMI). ~28% of the sample had LV hypertrophy. Marked differences in plasma leptin concentrations were noted between men and women. Thus, multivariate regression analysis was employed to identify independent relations between plasma leptin concentrations and either LVMI or LV mean wall thickness in sex-specific groups.

Before adjustments for potential confounders, plasma leptin concentrations were associated with LVMI in both women ($r=0.25$, $p<0.0001$) and in men ($r=0.20$, $p=0.017$) as well as with LV mean wall thickness in both women ($r=0.22$, $p<0.001$) and in men ($r=0.27$, $p=0.002$). Moreover, participants with LV hypertrophy defined as an LVM index of >51 g/m^2 had markedly greater plasma leptin concentrations than those participants without LV hypertrophy. However, plasma leptin concentrations were also associated with age, conventional systolic blood pressure and with adiposity indices ($p<0.0001$),

factors that had robust relationships with LVMI and LV mean wall thickness. In multivariate regression models with plasma leptin concentrations, adiposity indices, age, systolic blood pressure and a number of alternative potential confounders in the same regression model, although adiposity indices were strong independent predictors of both LVMI and LV mean wall thickness in both women and men ($p<0.002$-$p<0.0001$), plasma leptin concentrations were not independently related to either LVMI ($p=0.32$-0.96), or LV mean wall thickness ($p=0.33$-0.81). In conclusion, plasma leptin concentrations, although associated with, are not independent predictors of LVMI beyond adiposity indices and other related factors in a population sample with a high prevalence of excess adiposity. Therefore, plasma leptin concentrations are unlikely to predict cardiovascular risk beyond conventional risk measurements because of an impact on LVM.

DECLARATION

I declare that this dissertation is my own, unaided work. It is being submitted for the degree of Master of Science in the Faculty of Medicine, University of the Witwatersrand, Johannesburg. The work contained in this dissertation has not been submitted for any degree or examination in this university, or any other university.

.....

Neil Doodthnath Sookoo

.....25th.....day of .....MARCH....., 2009

I certify that the studies contained in this thesis have the approval of the Committee for of the University of the Witwatersrand, Johannesburg. The ethics number is M02:04-72 (renewed as M070469).

.....

Neil Doodthnath Sookoo

.....25th.....day of .....March....., 2009

....

Gavin R. Norton (Supervisor) Angela J Woodiwiss (Supervisor)

TABLE OF CONTENTS

Page

DEDICATION

This dissertation is dedicated to my wife, Marion Sookoo

ACKNOWLEGMENTS

I am very grateful to my supervisors, Professor's Gavin Norton and Angela Woodiwiss for their support and guidance as well as to the Medical Research Council (MRC), the National Research Foundation (NRF), Circulatory Disorders Research Fund (CDRF), the Belgium Government (Grant BIL01/43) and the University Research Council who supported the African Program on Genes in Hypertension (APOGH).

LIST OF ABBREVIATIONS

BMI: body mass index

BP: blood pressure

CHD: coronary heart disease

CHF: congestive heart failure

CV: cardiovascular

CVD: cardiovascular diseases

DBP: diastolic blood pressure

DM: diabetes mellitus

ELISA: enzyme-linked immunosorbent assay

g: grams

HbA1c: glycosylated haemoglobin

HDL: high density lipoprotein

Hg: mercury

IVS: inter-ventricular septal wall thickness

Kg: kilogram

LIFE: Losartan Intervention For Endpoint Reduction in hypertension

LV: left ventricular

LVED: left ventricular end diastolic

LVEDD: left ventricular end diastolic diameter

LVES: left ventricular end systolic

LVESD: left ventricular end systolic diameter

LVH: left ventricular hypertrophy

LVM: left ventricular mass

LVMI: left ventricular mass index

m: meter

MHz: Megahertz

MI: myocardial infarction

Mm: millimeter

MWT: end-diastolic mean wall thickness

ng: nanogram

NHSL: South African National Health Systems Laboratories

NO : Nitric oxide

PWT: posterior wall thickness

QC: quality control

RAAS: renin-angiotensin-aldosterone system

SBP: systolic blood pressure

SD: standard deviation

SK: skin-fold thickness

SOWETO: South Western Township

USA: United States of America

WC: waist circumference

WHR: waist-to-hip ratio

X: chi

LIST OF TABLES

Page

LIST OF FIGURES

Page

Chapter 2

Chapter 3

Page

PREFACE

Epidemiological surveys suggest that obesity is likely to become one of the major public health problems of the present century. Of the complications of obesity, cardiovascular disease, including strokes, myocardial infarction and heart failure, play a major role in obesity-induced morbidity and mortality. Although it is well accepted that obesity contributes toward cardiovascular disease by promoting the development of conventional cardiovascular risk factors including hypertension, dyslipidaemia and type II diabetes mellitus, there is increasing evidence to suggest that excessive adipose tissue may promote adverse effects on the cardiovascular system, which are not necessarily accounted for by conventional cardiovascular risk factors. One such effect is through an impact on left ventricular hypertrophy, a cardiovascular change that is a strong and independent predictor of cardiovascular morbidity and mortality.

Although there are a number of hypotheses that may explain obesity-induced effects on left ventricular growth, more recently there has been a suggestion that substances released from adipose tissue, such as the adipokine, leptin, may promote cardiac hypertrophy. In this regard, in the hopes of identifying obese people at risk of excessive cardiovascular target organ changes, a few studies have been performed to assess the independent relations between plasma leptin concentrations and left ventricular mass and geometry. The outcomes of these studies have been inconsistent and difficult to interpret due to the small number of participants studied, the extreme nature of the degree of obesity studied, or in larger studies conducted at a population level, the relatively low prevalence of obesity noted in the populations sampled. Thus, in the present dissertation, I assessed the independent relationship between plasma leptin concentrations and left ventricular mass and wall thickness in a randomly selected sample (n=378) of a community with a high prevalence of excess adiposity (~63%).

The present dissertation is presented as a series of chapters that guide the reader first through the background and purpose of the study (Chapter 1), then through the methods employed (Chapter 2), subsequently through the results of the present study (Chapter 3) and finally through a summary of the data, a discussion of the data in the context of previous studies, and the strengths and limitations of the present study (Chapter 4). In chapter 1, the present evidence to suggest that cardiac hypertrophy is a predictor of cardiovascular risk beyond alternative cardiovascular risk factors is reviewed. Thereafter, our present understanding of the role of obesity as a determinant of cardiac hypertrophy and the potential mechanisms thereof is reviewed.